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Report on the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage

SECTION V, PART I

Natural History of Subarachnoid Hemorrhage, Intracranial Aneurysms and Arteriovenous Malformations*

Based on 6368 Cases in the Cooperative Study

HERBERT B. LOCKSLEY, M.D.†

Introduction

The true natural history of a disease is notoriously difficult to delineate and in some respects exasperatingly elusive. It requires that observations be made on a sufficiently large sample of the disease population to accommodate natural variability, that this sample be representative of the total population of the disease and that the total disease population can be numerically related to the population-at-large. The natural course of the disease is elusive because of an obstacle which in present-day medicine amounts to a contradiction: the representative sample population must come under close medical scrutiny and at the same time not have its natural course modified by treatment!

Before the age of angiography, studies of the natural history of subarachnoid hemorrhage (SAH) and its various causes were necessarily founded on autopsy findings, and little could be done to establish the cause in those who lived. Angiography made possible the diagnosis of most aneurysms and arteriovenous malformations (AVM) in the living; surgical treatment soon became the order of the day, and the opportunity to obtain an unselected series of cases of SAH, aided by angiography and unmodified by treatment, rapidly receded.

Much is already known about the natural history of SAH and is a part of everyday teaching and clinical judgment. Recent knowledge is due in large part to a number of outstanding studies (Walton '53, McKissock *et al.* '58, '59, '60, Höök and Norlén '63,'64). A general survey of the literature has been presented by Sahs *et al.* '66, in Section I of the reports of this Cooperative Study.

Among the 6368 cases accumulated by the Central Registry of the Cooperative Study, subarachnoid hemorrhage occurred in 5831. Intracranial aneurysms were found in 2951 cases, and cerebral arteriovenous malformations in 353. These 6368 cases are analyzed here as an approximation to various aspects of the "natural history" of subarachnoid hemorrhage and its major causes. This analysis is, in fact, an accurate history of these diseases in the Study. How close an approximation these data are to true natural history in the general population cannot be stated, as there is no existing basis for comparison. Some general comments can be made, however, about the sample population of the Study in terms of the basic requirements for a natural history outlined above.

The sample population of the Cooperative Study is a large one by any previous standards for these diseases and would seem to be large enough to accommodate most natural variability. It was drawn from 19 University

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Medical Centers in the United States, and one center serving a large segment of the population of greater London. It seems a reasonable assumption that each participating center observed in its own locale a fairly representative sample of the SAH population in whom an angiographic or autopsy diagnosis of etiology was established. However, as a number of cases in each locale undoubtedly died too soon for referral to a participating center to be accomplished, early fatalities are probably under-represented. In other respects, the Study population appears to be acceptably representative of the general population of SAH.

Two considerations still impede the approach to a true natural history through the Cooperative Study data. First, information is lacking as to what fraction of the total SAH population is represented here. This precludes any calculations of the incidence of SAH and its causative lesions in the general population. Second, considerable distortion of the sample population has occurred through the non-random introduction of special treatments. This factor complicates and compromises the analysis of the natural course of these diseases, especially that of aneurysm. This latter problem has been mitigated, however, by the fact that the London center, under the leadership of Mr. Wylie McKissock, elected in 1958 to undertake a scientifically designed study of aneurysm treatment in which patients were randomly selected for surgical versus conservative treatment (McKissock *et al.* '58). This has provided the Study with a sizeable group of patients in whom the course of the disease was essentially uninfluenced except for bed rest. This group has been augmented by cases from other centers which elected or preferred treatment by bed rest alone. As bed rest is probably a natural consequence as well as a treatment of acute subarachnoid hemorrhage, these cases provide an almost ideal basis for study of long-term natural course. A special study of aneurysm treatments, begun in the Cooperative Study in 1963, randomly allocates cases to 4 treatment categories including bed rest. The 25 per cent of cases in this latter category can be expected, in time, to refine further our understanding of natural course..

Age of Onset of First Subarachnoid Hemorrhage

Of the 5831 cases with SAH in the Study, 4880 (83 per cent) were admitted following their first episode of SAH. These have been classified, on the basis of angiographic or autopsy evidence, into three main etiologic categories: aneurysm; arteriovenous malformation (AVM); and SAH of "other cause" (also referred to as "other SAH"). This latter category is a heterogeneous assemblage of diseases associated with SAH after aneurysm and AVM have been excluded by angiography and autopsy, and has been analyzed extensively in Section III (Locksley *et al.* '66). The frequencies of major causes of SAH in the Study are summarized in Table 49.

It is appropriate to begin the study of natural history with the questions: (1) "At what age are patients afflicted with their first SAH?"; (2) "What influence does etiology have on the age of onset?"; and (3) "Is there any difference between the sexes as to incidence and age of onset?"

In Table 50, the frequency of onset of SAH is tabulated by 5-year intervals for all cases admitted with first SAH and studied by angiography, autopsy or both. These cases are then analyzed in parallel according to the three major diagnostic categories. For convenience of visualization, the data are also presented graphically in Figure 42.

Considering all cases presenting with first SAH regardless of etiology, the data show that the great majority occurred in the second half of the normal life span. Moreover, 62 per cent bled between the ages of 40 and 60, the years of greatest responsibility and earning capacity. The peak frequency is seen to lie between ages 55 and 60 (Table 50).

TABLE 49

Frequency of Major Causes of Subarachnoid Hemorrhage in the Cooperative Study*

Intracranial aneurysms only	51%
Hypertensive and/or arteriosclerotic vascular disease	15%
Arteriovenous malformations only	6%
Miscellaneous or multiple casuses	6%
Cause indeterminate (by history plus angiography or autopsy)	22%

* Based on 5431 cases with angiographic or autopsy study.

TABLE 50

TABLE 50

AGE AND SEX DISTRIBUTION OF PATIENTS WITH FIRST SUBARACHNOID HEMMORRHAGE

Age	All First SAH					Aneurysm					Arteriovenous Malformations					Other First SAH				
	Total	%	M	F	Sex Ratio*	Total	%	M	F	Sex Ratio*	Total	%	M	F	Sex Ratio*	Total	%	M	F	Sex Ratio*
00–04	7	0.14	7	0		1		1	0		0		0	0		6	0.3	6	0	
05–09	15	0.14	7	8	M 1.7	6	0.2	1	5	—	3	1.1	3	0	—	6	0.3	3	3	M 3.0
10–14	30	0.61	23	7		7	0.3	6	1		12	4.4	9	3		11	0.6	8	3	
15–19	76	1.6	57	19	M 3.1	27	1.0	22	5	M 4.7	25	9.2	16	9	M 2.1	24	1.2	19	5	M 3.3
20–24	108	2.2	62	46		53	2.0	38	15		25	9.2	8	17		30	1.5	16	14	
25–29	137	2.8	78	59	M 1.3	60	2.3	41	19	M 2.3	29	10.7	14	15	F 1.5	48	2.4	23	25	M 1.0
30–34	230	4.7	142	88		122	4.6	81	41		32	11.8	16	16		76	3.8	45	31	
35–39	334	6.8	181	153	M 1.3	191	7.3	105	86	M 1.5	34	12.5	17	17	F 1.0	109	5.5	59	50	M 1.3
40–44	430	8.8	230	200		278	10.6	144	134		20	7.4	10	10		132	6.7	76	56	
45–49	635	12.9	329	306	M 1.1	369	14.0	176	193	M 1.0	31	11.4	19	12	M 1.3	235	11.9	134	101	M 1.3
50–54	670	13.7	331	339		407	15.5	183	224		16	5.9	9	7		247	12.5	139	108	
55–59	722	14.7	299	423	F 1.2	398	15.1	142	256	F 1.5	25	9.2	18	7	M 1.9	299	15.1	139	160	M 1.0
60–64	557	11.4	235	322		268	10.2	82	186		11	4.0	5	6		278	14.0	148	130	
65–69	439	9.0	138	301	F 1.7	233	8.9	46	187	F 2.9	4	1.5	2	2	F 1.1	202	10.2	90	112	M 1.0
70–74	268	5.5	63	205		130	4.9	13	117		5	1.8	1	4		133	6.7	49	84	
75–79	131	2.7	35	96	F 3.1	48	1.8	4	44	F 9.5					F 4.0	83	4.2	31	52	F 1.7
80–84	65	1.3	9	56		24	0.9	1	23							41	2.1	8	33	
85–89	19	0.39	2	17	F 6.6	4	0.15		4	F 27						15	0.8	2	13	F 4.6
90–94	7	0.14	2	5		1			1							6	0.3	2	4	
	4880		2230	2650		2627		1086	1541		272		147	125		1981		997	984	
			45.7%	54.3%				41%	59%				54%	46%				50.3%	49.7%	

* The prefix letter signifies Male or Female predominance in the sex ratio of that decade.

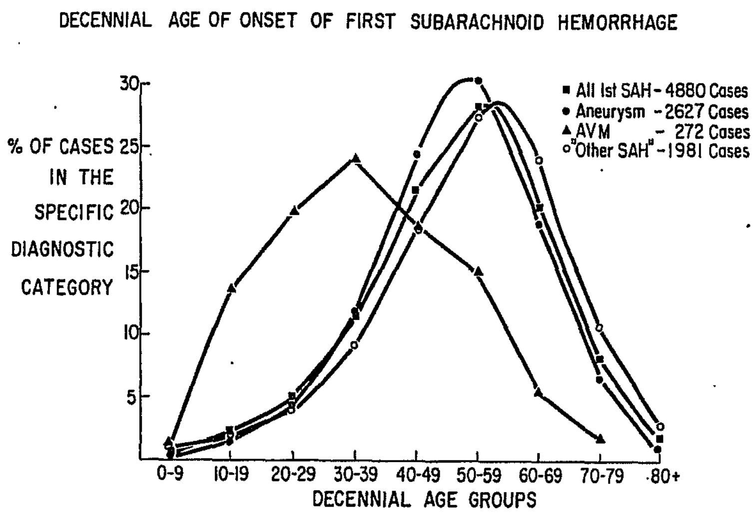


FIG. 42

When these cases of *first SAH* are segregated into diagnostic categories, intracranial aneurysms account for 54 per cent, AVM for 6 per cent, and "other SAH" for 40 per cent. Comparing the age distribution curves of each category, those for aneurysm and "other SAH" are similar in shape but with a shift in the curve of "other SAH" of about five years toward the older age group. The peak incidence of SAH from aneurysm appears to be 50 to 54 and that for "other SAH" 55 to 59.

The age distribution of first SAH from arteriovenous malformation is notably different. It spans the middle decades of life with a peak incidence from 30 to 40. Sixty-three (63) per cent of first bleeding episodes from AVM occurred from ages 20 to 49 and the other 37 per cent were nearly equally distributed on either side of this age bracket.

Figure 43 is an age-corrected version of the same data, taking into account the percentage of the aggregate population in each decennial age group as calculated from the 1960 U. S. census. The corrected curves present the frequency data as they would be derived from a population uniformly distributed in each decade, and equal in number to the decade 25 to 35 which contains the median age of 29.2 years. The age-corrected curves show a higher incidence in the decades over 60 and a more definite plateau in the frequency of onset of SAH due to arteriovenous malformation from 20 to 60. There is essentially no change in the shape of the curve for aneurysm from age 30 to 70, nor in its peak between 50 and 60.

Most Probable Cause of Subarachnoid Hemorrhage in any Given Decade

The clinical history and physical findings in a patient with SAH seldom give reliable clues as to the etiology. It is therefore of some interest to inquire whether there is a signifi-

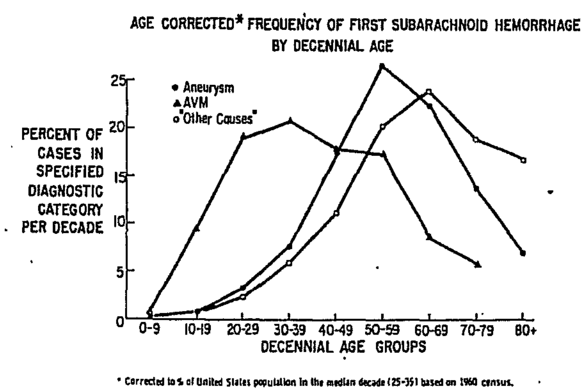
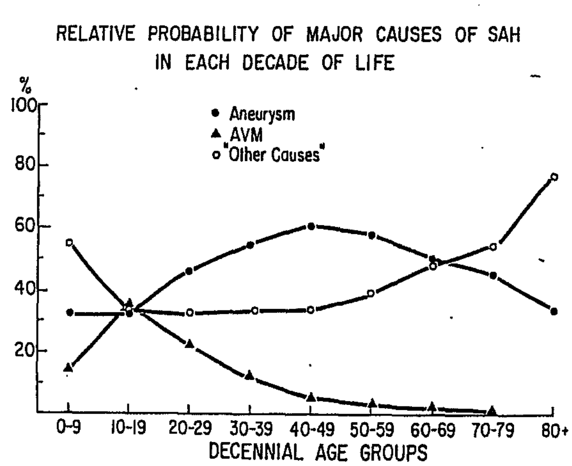


FIG. 43



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cant difference in probability of the major causes for various age groups. To answer this question, the age distribution data from Table 50 have been recalculated to give the relative percentage of aneurysm, AVM, and "other causes" for each decade (Figure 44). Between ages 20 and 69, aneurysm is the most probable cause of nontraumatic SAH. This diagnosis has the highest certainty in the decade 40 to 49 where the probability of aneurysm is nearly twice that of "other causes" and over 25 times that of AVM. Between 10 and 19, aneurysm, AVM, and "other SAH" are about equally probable. Aneurysm and "other SAH" are also about equally probable in the 'teens and in the 60's. Over age 70, "other SAH" predominates increasingly as hypertensive-arteriosclerotic SAH becomes more frequent and aneurysmal SAH declines. Arteriovenous malformation is never the most probable cause of SAH based on age alone, and is only a significant contender (probability greater than 1 in 5) in the second and third decades of life.

Relative Susceptibility of the Sexes to Spontaneous SAH

Table 50 demonstrates that 54 per cent of all cases with first SAH were women, 59 per cent of the aneurysm cases were women, and 54 per cent of AVM cases were men. There does not appear to be a significant sex difference in SAH of "other causes." The sex incidence of SAH for each major cause is not a simple relationship, however. When the sex ratio of SAH for each etiologic group is plotted by age decade (Figure 45), some interesting and unexpected findings may be observed.

It was noted above that overall, aneurysmal SAH occurs predominately in women in a ratio of about 3:2, but on examining the curve for aneurysm in Figure 45 it may be seen that men predominate in the age decades below 40. This male predominance exhibits a maximum ratio of 2.7:1 below age 20 and gradually diminishes to an equal sex incidence in the fifth decade. Above 50, women are preponderant and the ratio rises steeply from 3:1 at 60 to 69, to nearly 10:1 in the decade of the 70's.

In cases of SAH due to arteriovenous malformation, men tend to be more or less preponderant until the decade 70 to 79. It may be seen further, that the ratio of maximum

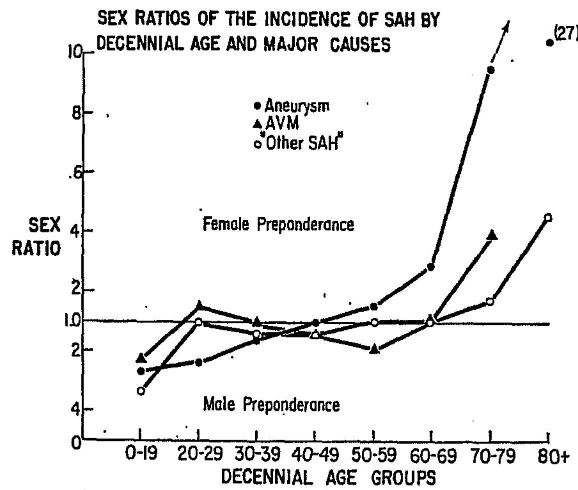

FIG. 45

male preponderance is 2.3:1 below age 20. This yields temporarily to women in the 20's, balances in the 30's, and again rises to almost 2:1 in the 50's.

For SAH of "other causes", the sex ratio is essentially unity between 20 and 70 except for a slightly enhanced susceptibility of males from 30 to 49. Below age 20, however, boys are preponderant in a ratio of 3.3:1. Above 70, women preponderate increasingly to reach a ratio of 4.6:1 from 80 to 90.

The increased susceptibility of women to SAH above 70 in all etiologic categories, and above 50 for aneurysm, is striking. Some of the observed differences may be accounted for by the sex-incidence of hypertension and numerical sex-differences in the population. The sex-ratios of hypertension by decennial age groups have been calculated from data of the United States National Health Survey collected from 1960–1962, and are presented in Table 51. This shows a preponderance of hypertension (*i.e.*, BP > 160 systolic) in men in early adult life changing to an increasing preponderance in women above age 45, and finally about the same sex incidence above age 75. Between ages 45 to 75, hypertension preponderates in women with a ratio of approximately 3:2.

Population sex-ratios, calculated from the 1960 United States census figures, are tabulated in Table 52. Overall the ratio of women to men in the general population is 1.03:1. Males show a slight preponderance below age 19. Thereafter, females predominate in the general population by a ratio of 1.05:1 between 20 and 59, 1.11:1 from 60 to 69,

TABLE 51

INCIDENCE OF HYPERTENSION BY SEX AND DECENNIAL AGE[1,2]

Age Group	Hypertensive Males			Hypertensive Females			Sex-Ratio
	No. of Cases	Per Cent Incidence	Median Systolic	No. of Cases	Per Cent Incidence	Median Systolic	F/M
18–24	15/7,139	0.21%	160	7/8,430	0.08%	160	—
25–34	109/10,281	1.06%	160–170	121/11,291	1.07%	160–169	1.0
35–44	590/11,373	5.2%	170–179	475/12,325	3.8%	160–169	0.73
45–54	891/10,034	8.9%	160–170	1,356/10,542	12.9%	170–179	1.45
55–64	1,284/7,517	17%	170–179	2,122/8,121	26%	170–179	1.53
65–74	1,443/4,972	29%	170–179	2,908/6,192	47%	180–189	1.62
75–79	581/1,428	41%	170–179	635/1,443	44%	170–179	1.07

[1] Calculated from U. S. National Health Survey Data from 1960–1962.
[2] Hypertension taken here to be a systolic blood pressure greater than 160 mm Hg.

1.21:1 from 70 to 79, and by 1.37:1 above age 80.

Assuming that the effect of age and hypertension are linear and independent of each other, these factors might account for a sex ratio of 1.76:1 (1.112×1.58) in the incidence of SAH for the decade of 60 to 69. This accounts for some, but not all, of the observed female preponderance of, for example, 2.1:1 among aneurysm cases. The basis of this sex

TABLE 52

U. S. POPULATION SEX RATIOS BY DECENNIAL AGE GROUPS[1,2]

Age Group	Males (49.25%)[2]		Females (50.75%)[2]		Sex Ratio	
	% of Males	% of Total	% of Females	% of Total	Females Per 100 Males	% Females in Age Group
00–19	39.7	19.55	38.4	19.49	99.7	49.9
20–29	12.0	5.91	12.2	6.19	104.7	51.2
30–39	13.5	6.65	13.7	6.95	104.5	51.1
40–49	12.5	6.16	12.6	6.39	103.7	51.0
50–59	10.1	4.97	10.1	5.13	103.2	50.8
60–69	7.2	3.56	7.8	3.96	111.2	52.7
70–79	4.0	1.97	4.7	2.38	120.8	54.7
80+	1.2	0.59	1.6	0.812	137.3	57.9

[1] Calculated from United States Census of Population: 1960 Vol. 1 Table 45.
[2] Total U. S. Population: 179,323,175.

TABLE 53

SYMPTOMS AND SIGNS ANTECEDENT TO FIRST SUBARACHNOID HEMORRHAGE

	All Aneurysm Cases[1]		Arterio-venous Malformation		Internal Carotid		Middle Cerebral		Anterior Communicating Region		Vertebral, Basilar, Posterior Cerebral	
Headache	1268	48%	115	43%	431	56%	195	43%	275	43%	48	50%
Orbital Pain	186	7%	17	6%	85	11%	21	5%	26	4%	7	7%
Diplopia	106	4%	7	2%	55	7%	11	2%	9	1%	5	5%
Ptosis	80	3%	1	—	53	7%	3	—	3	—	2	2%
Loss of Vision	103	4%	15	6%	42	5%	17	4%	17	3%	3	3%
Seizures	95	4%	35	13%	34	4%	15	3%	23	4%	3	3%
Motor or Sensory Disturbances	166	6%	36	13%	51	7%	24	5%	41	6%	9	9%
Dysphasia	45	2%	17	6%	17	2%	6	1%	4	—	2	2%
Bruit	78	3%	12	3%	26	3%	14	3%	16	3%	7	7%
Dizziness	272	10%	19	7%	89	11%	39	9%	59	9%	12	12%
Other (Misc.)	345	13%	67	23%	113	15%	62	14%	78	12%	9	9%
Total Cases	2621		270		775		452		637		96	

[1] Includes 521 cases with multiple aneurysms, 121 with proximal or distal anterior cerebral, and 19 with cerebellar artery aneurysms, in addition to the single aneurysm cases analyzed at the right.

difference obviously needs further pathologic and epidemiologic study.

Symptoms and Signs Antecedent to SAH from Aneurysm or AVM

The invariably serious threat, and frequently early fatality, associated with SAH from aneurysm and arteriovenous malformations give special importance to any advancement in our ability to identify these lesions before they rupture. Considering the antecedent symptoms for "all aneurysms" in Table 53, the only two symptoms with an incidence of at least 90 per cent are headache and dizziness, both of which are so commonplace and non-specific as to be of little diagnostic value. Even antecedent headache, which seems present so often in the history of patients prior to SAH, was not noted in over one-half (52 per cent). A similar and valuable analysis has also been made by Walker '56.

A comparison of the frequencies of various antecedent symptoms for specific aneurysm sites shows occasional small differences; but, in general, *the data support the impression, widely held, that aneurysm sites usually cannot be differentiated clinically except when the aneurysm becomes so large that it produces cranial nerve or other neighborhood signs of a space-taking lesion at the base of the brain.*

Environmental Events Related to the Onset of SAH

The question often arises as to what roles environmental stresses play in the "causation", "aggravation", or "precipitation" of subarachnoid hemorrhage. In Table 54, the frequencies with which various environmental events were noted to coincide with the onset of SAH are tabulated for patients subsequently shown to have aneurysm, AVM, or "SAH of other cause". A rigorous answer to this question just posed would require, in addition to data on the frequency of positive association of an environmental event, knowledge of the total number of people in each disease category with and without SAH, who were exposed to such stressful events and the duration of this exposure. This latter data is almost impossible to obtain and is not available. However, some relative estimates and inferences can be made which may prove helpful.

Referring to Table 54, the fact that so many cases in each diagnostic category bled during sleep indicates that SAH can, and frequently does, occur independently of any unusual environmental stresses. If we assume that one-third of our lives is spent in sleep, the fact that sleep was associated with the onset of SAH in about 33 per cent of cases in

TABLE 54

ACTIVITIES OR EVENTS RELATED TO THE ONSET OF SUBARACHNOID HEMORRHAGE

Type of Event	Aneurysm		AVM		"Other SAH"	
During sleep	820	36%	139	36%	746	38%
Unspecified circumstances	734	32%	108	28%	676	34%
Lifting or bending	273	12%	54	14%	172	8.7%
Emotional strain	100	4.4%	23	5.9%	87	4.4%
Defecation	99	4.3%	16	4.1%	67	3.4%
Coitus	87	3.8%	16	4.1%	44	2.2%
Coughing	49	2.1%	5	1.3%	44	2.2%
Trauma	63	2.8%	17	4.4%	59	3.0%
Urination	45	2.0%	6	1.5%	22	1.1%
Surgical operation	10	0.44%	2	0.51%	25	1.3%
Parturition	8	0.35%	2	0.51%	36	1.8%
Cases in Table 54	2288		338		1978	
Cases with no information	701		231		544	
Total cases with SAH	2989		519		2522	

each disease category suggests, further, that SAH occurs as a random event with respect to time of day. In approximately another third of each group, the onset of SAH coincided with miscellaneous environmental circumstances not specifically coded. This also tends to support the view that the association of environmental events with SAH is a random, coincidental one. However, the remaining one-third of the cases tends to deny that the onset of SAH is totally independent of environmental events, as the combination of all events specified would not seem to occupy one-third of the time for most people.

Minor trauma appears to have a notably greater association with onset of SAH from arteriovenous malformation (4.4 per cent). This may be due in part to the fact that AVM cases or arteriovenous malformations bleed more commonly in young people who are also more prone to vigorous activity. SAH occurred during coitus in 3.8 per cent of patients who bled from aneurysm, in 4.1 per cent of those bleeding from AVM, and in 2.2 per cent of those with "other SAH." The lower incidence in the last may be due to decreased sexual activity in this somewhat older-aged category. It is noteworthy that the frequency with which SAH is associated with coitus and defecation is about the same, and only one-half the frequency with micturition.[1]

Lifting and bending are among the commonest environmental events associated with the onset of SAH. There appear to be at least three factors of potential significance here: the Valsalva effect on venous pressure, the rise in arterial pressure with physical effort, and possible mechanical shifts of the brain and circle of Willis with respect to other fixed structures of the cranium such as tentorium and dura.

From a physiologic standpoint, the major long-term stress at a site of potential cerebral vascular weakness is the patient's blood pressure. Evidently, these forces alone, even in sleep, can eventually overcome the limits of elasticity of the lesion and result in hemorrhage; and by the same reasoning, environmental events which engender a chronic or acute elevation in blood pressure can be expected to hasten or precipitate this last critical step. On the other hand, considering the unremitting action of pulse and blood pressure, it would not be surprising if these two factors were found to have a more frequent association with the onset of SAH than any isolated environmental events. It would be of considerable value to demonstrate, in connection with this line of reasoning, whether patients with hypertension have a higher incidence of aneurysms than those who are normotensive; whether hypertensive aneurysm patients tend to bleed at an earlier age; and finally, if an age difference does

[1] It has been suggested that the true frequency of association between coitus and SAH may be somewhat higher than the figures reported here due to reticence in giving a history of this nature or retrograde amnesia when onset was associated with loss of consciousness.

exist, how much sooner an aneurysm would rupture in the presence of a 30 to 59 per cent over-normal elevation of blood pressure. Some data bearing on these questions will be presented in Section V, Part 2, in the discussion of unruptured aneurysms.

Site Distribution of Single Intracranial Aneurysms[1]

The 2695 cases of single aneurysm (ruptured and unruptured) in the Study have been analyzed for the frequency of various aneurysm sites, as well as sex incidence and lateralization at those sites (Table 55). A similar analysis (Table 56) provides parallel information for single aneurysms associated with subarachnoid hemorrhage. Cases with both aneurysm and AVM have been excluded from Table 56 because of uncertainty as to which was the source of hemorrhage. The data in these tables is self-explanatory, but a few points are of sufficient interest to warrant comment.

The commonest specific aneurysm site is the region of the anterior communicating artery[1] which accounted for 30 per cent of single *bleeding* aneurysms in the Study, followed in decreasing order by the region of the internal carotid-posterior communicating junction[1] which comprised 25 per cent and the region of the main middle cerebral branchings comprising 13 per cent.

It is frequently quoted that aneurysms arise most frequently from the internal carotid. That statement is also true for single aneurysm cases in the Cooperative Study when *all* internal carotid sites and non-

[1] As it is notoriously difficult to differentiate by angiography aneurysms which arise cleanly from the anterior communicating artery from those which involve the anterior cerebral junction, these sites have all been combined under the descriptive term "anterior communicating region." Similarly, the term "region of the posterior communicating junction" applied to internal carotid aneurysms connotes the inclusion of aneurysms arising from the posterior communicating artery within a few millimeters of the carotid and filling via the carotid system. Aneurysms arising from the posterior communicating-posterior cerebral junction are considered separately as a part of the vertebral-basilar system.

TABLE 55

Site Distribution of All Single Intracranial Aneurysms[1]

Aneurysm Site	No.	% of Total	Sub-Total	% of Total	M	F	Rt.	Lt.
Internal Carotid								
Foramen lacerum	2	—			2	0	1	1
Intracavernous[2]	50	1.9%			6	44	21	29
Below posterior communicating[3]	143	5.4%			36	107	65	78
Region of post. comm. junction[4]	670	25.0%			214	456	372	298
Posterior comm. to bifurcation[5]	121	4.5%			36	85	69	52
Bifurcation of internal carotid	118	4.4%			45	73	65	53
			1104	41.2%	339	765	593	511
					31%	69%	54%	46%
Anterior Cerebral								
Proximal to anterior communicating	41	1.5%			25	16	22	19
Anterior communicating region	747	28.0%			435	312	—	—
Distal to anterior communicating	69	2.6%			27	42	34	35
Segment not specified	38	1.4%			21	17	18	20
			895	33.5%	508	387	74	74
					57%	43%	50%	50%

(*Continued on following page*)

[1] Includes 56 cases with both aneurysm and arteriovenous malformation. Not included are 2 aneurysms of the carotid in the neck, 1 of the external carotid system, 3 "aneurysms" of the vein of Galen, 4 carotid-cavernous fistulas without demonstrated aneurysm, and 13 cases with unproved aneurysms or no site code.

[2] Includes 12 incidental aneurysms, 2 with related SAH, and 4 with cavernous fistula.

[3] Most of these aneurysms arise near the ophthalmic artery junction.

[4] Includes aneurysms of posterior communicating near the carotid junction and filling via the carotid system.

[5] Most of these arise near the anterior choroidal artery.

TABLE 55—*Continued*

Aneurysm Site	No.	% of Total	Sub-Total	% of Total	M	F	Rt.	Lt.
Middle Cerebral								
Proximal to main branchings	97	3.6%			36	61	51	46
Region of main branchings	324	12.1%			131	193	184	140
Distal to main branchings	37	1.4%			20	17	21	16
Segment not specified	71	2.7%			30	41	43	28
			529	19.8%	217 41%	312 59%	299 57%	230 43%
Posterior Cerebral								
Main trunk	7				3	4	6	1
At basilar junction	4				3	1	2	2
Segment not specified	11				5	6	3	8
			22	0.8%	11 50%	11 50%	11 50%	11 50%
Basilar								
Apical bifurcation	48	1.8%			24	24	—	—
Main trunk	29	1.1%			18	11	—	—
			77	2.9%	42 55%	35 45%	— —	— —
Vertebral								
Proximal to basilar	10				3	7	7	3
At basilar junction	4				4	0	3	1
Segment not specified	11				4	7	8	3
			25	0.9%	11 44%	14 56%	18 72%	7 28%
Cerebellar								
Posterior inferior	13				6	7	6	7
Superior cerebellar	7				1	6	4	3
Anterior cerebellar	—				—	—	—	—
			20	0.7%	7 35%	13 65%	10 50%	10 50%
Totals	2672	100%			1135 43%	1537 57%	1005 54%	843% 46%

bleeding as well as bleeding aneurysms are included.

Aneurysms of the posterior circulation including the intracranial portion of the vertebral arteries, basilar, posterior cerebral and cerebellar arteries made up 5.5 per cent of the total. The commonest site on the posterior circulation was the basilar apex followed by basilar trunk and posterior inferior cerebellar arteries.

There is an apparent preponderance of aneurysms on the right side for most major sites, with an overall right-sided incidence of 55 per cent. Whether this represents a true anatomic difference in susceptibility of the two sides or is due to exclusion of some left-sided cases from referral to the reporting centers because of disheartening aphasia, remains an open question. The fact that the greatest right-sided preponderance (58 per cent) in the carotid system is found with middle cerebral aneurysms tends to support the latter interpretation.[1]

[1] Another factor considered is the preference of angiographers for starting on the right side. Single aneurysm cases diagnosed by unilateral carotid angiography were analyzed for the incidence of right and left lateralization. Of the 339 cases, 56 per cent had right carotid angiography only, which is about the same incidence as right-sided aneurysms. The 339 cases are far too few, however, to account for the right-sided preponderance in 2672 cases.

Rt.	Lt.
51	46
184	140
21	16
43	28
299	230
57%	43%
6	1
2	2
3	8
11	11
50%	50%
—	—
—	—
—	—
—	—
—	—
7	3
3	1
8	3
18	7
72%	28%
6	7
4	3
—	—
—	—
10	10
50%	50%
1005	843%
54%	46%

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TABLE 56

SITE DISTRIBUTION OF SINGLE ANEURYSMS ASSOCIATED WITH SUBARACHNOID HEMORRHAGE

Aneurysm Site	No.	% of Total	Sub-Total	% of Total	M	F	R	L
Internal Carotid								
Intracavernous[1]	2	—			—	2	—	2
Below posterior communicating	101	4.3%			25	76	42	59
Region of post. comm. junction	576	25.0%			186	390	321	255
Posterior comm. to bifurcation	101	4.3%			32	69	57	44
Bifurcation of internal carotid	106	4.5%			41	65	54	52
			886	38%	284	602	474	412
					32%	68%	54%	46%
Anterior Cerebral								
Proximal to anterior communicating	35	1.5%			21	14	20	15
Anterior communicating region	711	30.3%			412	299	—	—
Distal to anterior communicating	66	2.8%			26	40	32	34
Segment not specified	36	1.5%			19	17	18	18
			848	36%	478	370	70	67
					56%	44%	51%	49%
Middle Cerebral								
Proximal to main branchings	91	3.9%			33	58	47	44
Region of main branchings	307	13.1%			122	185	176	131
Distal to main branchings	32	1.4%			17	15	18	14
Segment not specified	58	2.5%			23	35	40	18
			488	21%	195	293	281	207
					40%	60%	58%	42%
Posterior Cerebral								
Main trunk	7	—			3	4	6	1
At basilar junction	4	—			3	1	2	2
Segment not specified	10	—			5	5	2	8
			21	0.9%	11	10	10	11
Basilar								
Apical bifurcation	48	2.0%			24	24	—	—
Main trunk	19	0.8%			11	8	—	—
			67	2.9%	35	32	—	—
Vertebral								
Proximal to basilar	8	—			2	6	6	2
At basilar junction	3	—			3	—	2	1
Segment not specified	9	—			2	7	6	3
			20	0.9%	7	13	14	6
Cerebellar								
Posterior inferior	11	—			5	6	4	7
Superior cerebellar	6	—			1	5	3	3
Anterior cerebellar	2	—			—	2	2	—
			19	0.8%	6	13	9	10
Totals	2349	100%			1016	1333	858	713
					43%	57%	55%	45%

[1] Intracavernous aneurysms with supracavernous extensions and SAH. Excludes 11 cases with carotid-cavernous fistula interpreted by the computer as SAH.

TABLE 57

PROBABILITY OF SINGLE ANEURYSM SITES AMONG MALES AND FEMALES WITH BLEEDING AND NON-BLEEDING ANEURYSMS

Aneurysm Site	Bleeding Aneurysms			Non-Bleeding Aneurysms		
	% of Aneurysm	% of Males	% of Females	% of Aneurysms	% of Males	% of Females
Anterior Communicating Region	30	41	22	12	20	7
Posterior Communicating-Carotid Junction Region	25	18	29	29	23	32
Middle Cerebral at Main Branchings	13	12	14	6	8	4
All Internal Carotid Sites	38	28	45	64	44	76
All Anterior Cerebral Sites	36	47	28	16	26	9
All Middle Cerebral Sites	21	19	22	14	19	10
All Posterior Circulation Sites	5.5	6	5	6	10	4

The widespread impression that aneurysms are more frequent in women is borne out by the finding in the Cooperative Study that 56 per cent of single bleeding aneurysms occurred in women. That this female preponderance is even higher for non-bleeding aneurysms will be shown later. Even more revealing, however, is the correlation between sex incidence and aneurysm site. Internal carotid aneurysms occur in women more than twice as frequently as in men. Middle cerebral aneurysms are also more frequent in women, in the ratio of 3:2. On the other hand, anterior communicating aneurysms are more frequent in men, who comprise 58 per cent of the cases at this site.

Site Probabilities in Cases with Bleeding and Non-bleeding Single Aneurysms

When a patient with first subarachnoid hemorrhage is admitted for diagnostic work-up, we have seen that the chances of an aneurysm being found are 54 per cent. Can we now make any prediction as to the most likely site of the aneurysm from the foregoing data? In Table 57 (derived from data in Tables 55 and 56), the probability is given for discovering an aneurysm at the commoner sites by sex when the cause of bleeding is aneurysm. If the sex of the patient is not immediately known, the most likely site is anterior communicating (probability, 30 per cent) followed by the region of the posterior communicating junction (25 per cent) and the main branchings of the middle cerebral (13 per cent). If the patient is male, the most probable site is anterior communicating (41 per cent) and this probability is more than twice as great as for any other specific site. On the other hand, if the patient is female, the most probable site of aneurysm is the region of the internal carotid-posterior communicating junction. In general, for males, the chances of the aneurysm arising somewhere along the course of the anterior cerebral artery is nearly 50:50 (48 per cent); and for females the chances of some portion of the internal carotid being involved is 43 per cent.

Parallel probability data are presented for unruptured aneurysms in Table 57 and show even greater differences in site and sex distributions. Perhaps the outstanding feature of these data is the strong predominance of the internal carotid site group which is the site of unruptured aneurysm in 76 per cent of the females and 44 per cent of the males. It should be noted that this data for non-bleeding aneurysms strongly reflects the high propensity of aneurysms at certain sites to reveal themselves symptomatically before bleeding occurs, in addition to the differences in site susceptibility of the sexes.

It has been shown (Figure 45) that there are some striking variations in the sex-incidence of aneurysms as a function of patient age, and we have seen here that notable variations occur in the sex-incidence of aneurysms at various sites. An attempt is made to correlate and extend the analysis of these two

TABLE 58

COMPARISON OF THE SEX INCIDENCE OF SINGLE ANEURYSMS ACCORDING TO SITE AND DECENNIAL AGE

Aneurysm Site		Decennial Age Groups and Sex Incidence Ratios							
		00–19	20–29	30–39	40–49	50–59	60–69	70–79	Total
Internal Carotid-Ophthalmic Region	M	—	3	1	3	3	—	—	10
	F	1	—	6	12	16	10	2	47
Internal Carotid-Posterior Communicating	M	1	4	21	29	35	13	2	105
	F	—	11	35	69	71	49	9	244
	F/M	—	3:1	5:3	7:3	2:1	4:1	4:1	7:3
Internal Carotid-Choroidal Region	M	3	1	2	3	5	3	1	18
	F	1	1	10	8	7	11	2	40
Internal Carotid Bifurcation	M	—	2	4	5	8	3	—	22
	F	—	5	1	11	8	15	1	41
All Internal Carotid	M	4	10	28	40	51	19	3	155
	F	2	17	52	100	102	85	14	372
	F/M	1:2	1.7:1	1.9:1	2.5:1	2:1	4.5:1	4.7:1	2.4:1
Middle Cerebral	M	5	14	36	65	66	27	4	217
	F	7	12	41	95	83	60	12	310
	F/M	1.2:1	1:1.2	1.1:1	1.5:1	1.3:1	2.2:1	3:1	1.4:1
Anterior Communicating Region	M	12	38	70	117	143	50	6	436
	F	4	14	48	58	99	67	21	311
	F/M	1:3	1:2.7	1:1.5	1:2	1:1.4	1.3:1	3.5:1	1:1.4
Basilar Bifurcation	M	2	1	3	12	6	1	1	26
	F	1	—	2	9	9	4	—	25

phenomena of sex-incidence in Table 58. Here all single aneurysm cases are broken down into major sites, and the sex-incidence compared for each decennial age period. Thus, for example, one can read horizontally the ratios of sex-incidence for anterior communicating aneurysms for any decade from 20 to 80.

For internal carotid aneurysms, where females predominate with a ratio of 2.4:1 overall, there is, in fact, a male preponderance below age 20. Similarly, for anterior communicating aneurysms, males predominate with a ratio of 1.4:1 overall; but male predominance applies only up to age 59, after which females predominate increasingly. In the case of middle cerebral aneurysms, females predominate overall, but there appears to be no significant sex difference from 20 to 39.

These data on sex and age incidence appear highly relevant to the pathophysiology of aneurysms. It is hoped that they will prove helpful in future studies of the cause(s) and development of aneurysms, and, in turn, be explained by the furthering of our understanding of aneurysm pathogenesis.

Relative Frequencies of Single and Multiple Aneurysms

All aneurysm cases in the Study (including those with an associated arteriovenous malformation) were analyzed for the relative frequencies of single and multiple aneurysms. The analysis was made in three different ways based on the methods employed in establishing the diagnosis: (1) aneurysm defined by angiography only; (2) those defined by autopsy only; and (3) all cases, using the maximum information available, including evidence from angiography, operation, and autopsy.

Each of the methods of analysis has its limitations. Diagnosis by angiography here does not imply total angiography; hence the incidence of multiple aneurysms from angiography alone is likely to be on the low side. If

TABLE 59

FREQUENCY OF SINGLE VERSUS MULTIPLE ANEURYSMS

Methods of Study	No. of Aneurysms Per Patient	No. of Cases	% of Total	% Multiple
Maximum Data (Angiography, Surgery, Autopsy)	1	2695	81%	
	2	462	14%	
	3	117	3.5%	19%
	4 or more	47	1.4%	
	Total	3321	100%	
Angiography Data Only	1	2553	81%	
	2	453	14%	
	3	109	3.4%	18.5%
	4 or more	36	1.1%	
	Total	3151	100%	
Autopsy Data Only	1	693	78%	
	2	149	17%	
	3	35	3.9%	22%
	4 or more	11	1.2%	
	Total	888	100%	

patients with multiple aneurysms are assumed to have a higher mortality than those with single aneurysms (noted later to be 2 per cent higher); then autopsy data would tend to give an erroneously high frequency for multiple aneurysms. On the other hand, some aneurysms may be destroyed by bleeding prior to autopsy, and others may be missed in routine dissections, in consequence of which the autopsy data on multiple aneurysms may be too low. Considering the data together, however, they probably set reasonable upper and lower limits on the incidence of single and multiple aneurysms in the general aneurysm population.

The range of figures obtained for the incidence of multiple aneurysms is 18.5 per cent by angiography alone, to 22 per cent based on autopsy findings (Table 59). A reasonable estimate for the incidence of multiple aneurysms from these data might be 20 per cent. Figures in the literature range from 8 to 30 per cent (Poppen and Fager '59, McKissock *et al.* '64, Heiskanen '65, Overgaard and Riishede '65).

Of all the aneurysm cases in the Study, about 3.5 per cent had 3 aneurysms and about 1.4 per cent had 4 or more.

Site Correlations in cases of Multiple Aneurysm

In the foregoing, the site frequencies of single aneurysms, and probability of occurrence of multiple aneurysms, have been considered. This leads to a further question of some practical importance: "What is the probable site of a second aneurysm once the first aneurysm has been identified?" The answer to this question would be of assistance in estimating how far cerebral angiography should be pursued in a given case, and might also shed some light on the underlying pathophysiology of aneurysm formation.

Without evidence to the contrary, it appears reasonable to assume, as a beginning hypothesis, that the sites of multiple aneurysms are independent of one another (except, of course, that 2 cannot occur at exactly the same place), and that the most probable site for the second aneurysm is the same as most probable site in single aneurysm cases. Since internal carotid is the most probable general location for a single aneurysm, this hypothesis would lead us to predict that regardless of the site of the first aneurysm (*e.g.*, anterior communicating) the most probable site of the second aneurysm is internal carotid.

Test of the Hypothesis of Independence of Double Aneurysm Sites

This hypothesis can be tested quite simply by calculating the predicted frequencies of individual aneurysms at various sites per 100 cases, and then comparing these predictions with the observed site-frequencies of individual aneurysms among double aneurysm cases in the Study. According to the hypothesis, the *predicted frequency* of aneurysms at each site is the same whether single or double aneurysm cases are considered (Columns 1 and 2 in Table 60). Comparing with the observed frequencies (Column 3), it is seen that there is no correspondence between the two sets of data. The observed frequencies are substantially higher for internal carotid and middle cerebral aneurysms, about one-half the predicted frequency for anterior communicating and somewhat less for the other sites. *These data indicate that the hypothesis of independence of double aneurysm sites is untenable.* The probability that this inconsistency of the data is a mere chance occurrence, and that the hypothesis may in fact be correct, is less than 1 per cent ($p < .01$).

While other hypotheses regarding the probable association of double aneurysms could be made, they cannot be tested so easily by total aneurysm counts. It was de-

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TABLE 60

TEST OF THE HYPOTHESIS THAT SITES OF DOUBLE ANEURYSMS ARE INDEPENDENT OF EACH OTHER[1]

Predicted and Observed Site Frequencies in 449 Double Aneurysm Cases

	Observed Frequencies in All Single Aneurysm Cases		Hypothetical Frequencies in Double Aneurysm Cases	Observed Frequencies in Double Aneurysm Cases	
Internal Carotid	1104	41%	41%	428	48%
Anterior Communicating	747	28%	28%	124	14%
Middle Cerebral	529	20%	20%	265	30%
Vertebral-Basilar, Post. Cerebral, Cerebellar	144	5.3%	5.3%	40	4.5%
Proximal and Distal Anterior Cerebral	148	5.5%	5.5%	41	4.6%
Total	2672	100%	100%	898	100%

[1] A chi-square test of the data indicates that the hypothesis of independence is rejected at a significant level of $p<.01$.

cided therefore to undertake a determination of the observed frequencies of aneurysm site association for all cases in the Study reported to have two and only two aneurysms. Cases of greater aneurysm multiplicity were avoided as they would greatly increase the complexity of the analysis.

Probable Site of Second Aneurysm When One Has Been Found

All cases reported to have two aneurysms were segregated on the basis of the first aneurysm into seven site groups: (1) internal carotid, (2) middle cerebral, (3) anterior communicating region, (4) proximal anterior cerebral, (5) distal anterior cerebral, (6) vertebral-basilar-posterior cerebral system, and (7) cerebellar arteries. No lateral distinction was made for Groups 3, 6, and 7. A symmetrical two-dimensional matrix was then computer-produced which correlated the number of first aneurysms in each site group with the frequency of occurrence of similarly defined sites for the second aneurysms. This matrix included 463 cases of double aneurysm. Inspection of the protocols of those cases supposedly having two aneurysms at the same site revealed that 13 cases had the same aneurysms coded somewhat differently in the various fascicles and were counted twice, and in one case, the second aneurysm was really an AVM. The matrix was corrected for these 14 cases, leaving a total of 449. There still remain however, 55 cases with two bona fide aneurysms at nearly the same site of origin.

The method of site determination and the extent of angiography in these 463 cases were also investigated. The diagnosis of double aneurysm was established by autopsy in 144 cases (31 per cent) and 111 of these also had angiography. The diagnosis of double aneurysm was established only by angiography, in 319 cases (69 per cent); 96 per cent had at least bilateral carotid angiography and 13 per cent had studies of three or four major vessels. In 14 cases, multiple aneurysms were disclosed by unilateral carotid angiography, and it is possible that two or three cases might have shown more than two aneurysms had further studies been made. These 14 marginally studied cases comprise 3 per cent of the total series.

A summary of the two-dimensional matrix is presented in Table 61.

In analyzing this data, a convenient first question to ask is, "If the two aneurysms are lateralized (*i.e.*, neither aneurysm is anterior communicating or posterior circulation) what is the probability that the second aneurysm will be on the same side?" It was found (Table 62) that of the total number of double aneurysm cases (449), both aneurysms were on the same side in 93 (21 per cent), on opposite sides in 211 (47 per cent) on one side plus a midline aneurysm in 132 (29 per cent), and both midline in 13 (3 per cent). *Thus, for all doublets which do not include anterior communicating or posterior circle of Willis, the chances are greater than 2:1 that the aneurysms will be on opposite sides; furthermore, 47 per*

TABLE 61

CORRELATION OF DOUBLE ANEURYSM SITES

Site and Side of First Aneurysm		Total No.	Site of Second Reported Aneurysm							Lateralization of Second Aneurysm			Lateralization when both Aneurysms are the same Site Group		
			Internal Carotid	Middle Cerebral	Ant. Comm.	Proximal Anterior Cerebral	Distal Anterior Cerebral	Vertebral-Basilar Posterior Cerebral	Cere-bellar Arteries	Right	Left	Mid-line	Ipsi-lateral	Sym-metrical	Mid-line
Internal	Right	125	79	27	10	4	—	5	—	29	81	15	13	66	—
Carotid	Left	99	61	21	7	4	3	2	1	56	33	10	18	43	—
Middle	Right	72	17	40	10	2	3	—	—	13	49	10	5	35	—
Cerebral	Left	41	10	17	5	2	1	4	2	17	13	11	6	11	—
Anterior Communicating	Midline	82	27	39	7	3	3	3	—	32	40	10	—	—	7
Proximal Ante-	Right	6	2	3	—	—	—	—	1	3	2	1	—	—	—
rior Cerebral	Left	3	2	—	—	—	—	1	—	1	1	1	—	—	—
Distal Ant.	Right	4	—	3	—	—	1	—	—	1	3	—	—	1	—
Cerebral	Left	2	1	1	—	—	—	—	—	2	—	—	—	—	—
Vertebral-Basilar Post. Cerebral	[1]	15	5	1	3	—	—	5	1	2	4	9	—	—	6
Cerebellar Arteries	[1]	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		449	204	152	42	15	11	20	5	156	226	67	42	156	13

[1] No distinction made as to side; treated as "midline."

N.B. When calculating the total frequency of any given site-combination, one must add the frequencies obtained when each aneurysm of the combination is reported first; *e.g.*, middle cerebral-internal carotid=27, plus internal carotid-middle cerebral=48; giving a total of 75.

cent of all double aneurysms are contralateral to each other.

The incidence of various major site combinations, obtained from the matrix, and presented in Table 63, lead to the following observations:

1. *Combinations Involving Internal Carotid.* If an aneurysm of the internal carotid is identified, and the patient has a second aneurysm (chances 1 in 5), the data indicate that in 49 per cent the second aneurysm is also internal carotid. The chances of the two internal carotid aneurysms being symmetrically disposed, as compared with two on the same internal carotid, are greater than 3:1. However, when the second aneurysm is middle cerebral, the chances of it being ipsilateral or contralateral are about equal. Middle cerebral is the next most probable associated site (26 per cent) followed by anterior communicating (15 per cent). Considering that single anterior communicating aneurysms are 9 per cent more common

TABLE 62

PROBABILITY OF SAME VERSUS OPPOSITE SIDES IN DOUBLE ANEURYSMS

	No. of Cases	% of Total
Opposite Sides	211	47%
Same Side	93	21%
Midline and Side	132	29%
Both Midline	13	3%
	449	100%

TABLE 63

FREQUENCY OF SECOND ANEURYSM SITES WHEN ONE ANEURYSM HAS BEEN IDENTIFIED

Site of One Aneurysm[1]	Second Aneurysm Site[1]	Observed Frequency	Probability of Second Site × 100: Total	Ipsilateral	Contralateral
Internal Carotid	1. Internal Carotid	140	49%	11%	38%
	2. Middle Cerebral	75	26%	48%	52%
	3. Anterior Communicating	44	15%	—	—
	4. Prox. or Distal Ant. Cerebral	16	5.6%	2.8%	2.8%
	5. Posterior Circulation[2]	13	4.5%	—	—
		288	100%		
Middle Cerebral	1. Internal Carotid	75	36%	48%	52%
	2. Middle Cerebral	57	27%	5%	22%
	3. Anterior Communicating	54	26%	—	—
	4. Prox. or Distal Ant. Cerebral	15	7.2%	47%	53%
	5. Posterior Circulation[2]	7	3.4%	—	—
		208	100%		
Anterior Communicating	1. Middle Cerebral	54	46%	—	—
	2. Internal Carotid	44	38%	—	—
	3. Anterior Comm. Region	7	6%	—	—
	4. Posterior Circulation[2]	6	5%	—	—
	5. Prox. or Distal Ant. Cerebral	6	5%	—	—
		117	100%		
Posterior Circulation[2]	1. Internal Carotid	13	48%	—	—
	2. Posterior Circulation[2]	6	22%	—	—
	3. Anterior Communicating	6	22%	—	—
	4. Prox. or Distal Ant. Cerebral	2	7%	—	—
Totals		27	100%		

[1] The association of double aneurysm in this table is independent of the order of their discovery.
[2] As defined here, "posterior circulation" includes vertebrals, basilar, posterior cerebrals, and cerebellar arteries. No distinctions have been made as to side.

- No distinction made as to side; treated as midline.
N.B. When calculating the total frequency of any given site-combination, one must add the frequencies obtained when each aneurysm of the combination is reported first; *e.g.*, middle cerebral-internal carotid = 27, plus internal carotid-middle cerebral = 48; giving a total of 75.

than single middle cerebral, it is surprising that aneurysms of the internal carotid are associated with middle cerebral almost twice as often as with anterior communicating![1]

2. *Combinations Involving Middle Cerebral.* When a middle cerebral aneurysm has been identified, the most probable site of the second aneurysm is again internal carotid (36 per cent) followed about equally by middle cerebral and anterior communicating (27 per cent and 26 per cent respectively). When the second aneurysm is also middle cerebral, the chances are greater than 4:1 that it will be contralateral; but an associated internal carotid aneurysm is about equally likely to be ipsilateral or contralateral.

3. *Combinations Involving Anterior Communicating.* In contrast to the above, when an anterior communicating aneurysm has been demonstrated, the most probable associated site is middle cerebral (48 per cent) followed at some distance by internal carotid (38 per cent). Interestingly, *a second aneurysm of the anterior communicating region is as probable as one on the posterior circle. It is also noteworthy that of the three major sites, anterior communicating aneurysms are least likely to be associated with a second aneurysm.*

4. *Combinations Involving the Posterior Circulation.* In the presence of an aneurysm of the posterior circulation, the most probable site for a second aneurysm is internal carotid (48 per cent) followed equally by another on the posterior circulation (22 per cent) or anterior communicating (22 per cent). *When an aneurysm of the anterior circulation has been identified, the probability that the second aneurysm will be found on the posterior circulation is of the order of 3 to 5 per cent.*

Possible Factors Determining Site of Aneurysm Formation

In the foregoing, the hypothesis that the sites of origin of double aneurysms are independent of each other was rejected, and the frequencies with which various combinations of double aneurysms occur were determined empirically. It is pertinent to inquire whether the empirical data suggest a better hypothesis to explain the observed combinations, and what implications the new hypothesis might have regarding aneurysm formation. As no pattern clearly emerges from Table 63 which might lead to a new hypothesis, the following question was posed: "If the sites of double aneurysms are not independent of each other, in what respects and to what extent are they dependent upon each other?"

To answer this question, a table of the main double-aneurysm combinations and their predicted frequencies was calculated from a hypothetical symmetrical matrix, based again on the assumption that aneurysm sites are independent of each other and using the site incidence of single aneurysms for calculation. These hypothetical frequencies were then compared with the observed frequencies of double aneurysm combinations (See Table 64), and the ratios of observed to predicted frequencies calculated (right hand column).

These ratios clearly show that, when double aneurysms are both internal carotid, both middle cerebral, or both posterior circulation, the observed frequency of the combination is 2 to 4 times the hypothetical frequency based on independence of aneurysm sites. It is evident, therefore, that *whatever the factors may be which determine the site distribution of single aneurysms, they are greatly outweighed for internal carotid and middle cerebral aneurysms by a tendency toward either symmetrical aneurysms or the development of a second aneurysm on the same vessel.* Despite

TABLE 64

Comparison of Hypothetical and Observed Frequencies of Double Aneurysm Combinations

Double Aneurysm Combination[1]	Hypothetical Frequency of Combination Assuming Site Independence	Observed Frequency of Combinations	Approx. Ratio Obs./Hypoth.
IC—AC	23%	44 10.0%	1/2
IC—MC	16%	75 17.0%	1
IC—IC	15%	140 31.0%	2
MC—AC	12%	54 12.0%	1
AC—AC	8.4%	7 1.6%	1/5
IC—PC	4.3%	13 2.9%	2/3
MC—MC	4.0%	57 13.0%	3
AC—PC	3.2%	6 1.3%	1/2.5
MC—PC	2.2%	7 1.6%	3/4
PC—PC	0.3%	6 1.3%	4
All Others	11.4%	40 8.9%	9/11
	100%	449	

[1] IC=Internal Carotid, AC=Anterior Communicating, MC=Middle Cerebral, PC=Posterior Circulation.

[1] The argument that it is twice as great because there are two middle cerebrals to one anterior communicating fails because of the higher incidence of single anterior communicating aneurysms.

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0%	1
6%	1/5
9%	2/3
0%	3
3%	1/2.5
6%	3/4
3%	4
9%	9/11

mmunicating, MC

this, for internal carotid-middle cerebral, middle cerebral-anterior communicating, and double aneurysm combinations involving proximal or distal anterior cerebral (the main components of "all others" in the table), the observed frequencies are very close to the predicted frequencies. This suggests that these associations are random and coincidental.

All combinations involving an anterior communicating aneurysm, except those with middle cerebral, occur less often than the hypothetical frequency: 1/2 for internal carotid, 1/5 for double anterior communicating, and 1/2.5 for posterior circulation. The low incidence of two aneurysms in the same anterior communicating region can perhaps be explained by the very short segment of artery available, but the low incidence of the anterior communicating-internal carotid combination is surprising and not easily accountable. It might be argued that this is a reflection, not so much of the behavior of anterior communicating aneurysms but of the tendency of internal carotid aneurysms to symmetrical doubling. This explanation fails to some extent when one considers anterior communicating-middle cerebral aneurysms where the ratio is 1.0 in spite of the fact that double middle cerebral aneurysms occur three times as often as predicted. The other strange observation, requiring explanation, is the fact that anterior communicating aneurysms have a greater tendency than all others to appear singly. A likely factor bearing on these observations relates to sex incidence. It was noted earlier that anterior communicating aneurysms are preponderant in males by a ratio of 1.4:1, and that internal carotid aneurysms occur for the most part in females with a ratio greater than 3:1. Taken together, these differences in sex incidence and the strong tendency of internal carotid aneurysms to symmetrical doubling help to explain both the low incidence of the anterior communicating-internal carotid combination and the generally low incidence of double aneurysms involving an anterior communicating aneurysm.

The strong influence of symmetry in multiple aneurysms would seem to ascribe major roles to one or both of two factors in aneurysm development: (1) congenital, symmetrical, developmental weakness of the cerebral vessels, and (2) symmetrical circulatory dynamics of embryologic origin which facilitate aneurysm formation later in life. It has been demonstrated recently by Sahs '66 that congenital bifurcation defects in the muscle coat of cerebral vessels may predipose to aneurysm formation but are not *per se* sufficient condition for an aneurysm to occur. Sahs has also shown that the critical factor is a defect in the elastic lamina at aneurysm sites. Whether the latter are congenital or acquired is as yet unanswered.

Probable Effectiveness of Unilateral Versus Bilateral Angiography in Discovering Multiple Aneurysms

A question of considerable practical importance is the percentage of double aneurysm cases[1] which are potentially detectable by various degrees of angiographic study short of total cerebral angiography. In the Cooperative Study report on cerebral angiography (Perret and Nishioka '66) a direct, empirical approach to answering this question was found to be fraught with difficulties, due to the exercise of selective judgment in determining the extent of angiography performed in a given patient. This has led to the present indirect approach based on the observed frequencies of double aneurysm site-combinations in Table 61.

For this analysis, it is assumed that unilateral carotid angiography successfully demonstrates the ipsilateral carotid, middle cerebral, and anterior cerebral arteries and *also the anterior communicating segment*, and that all aneurysms present are angiographically demonstrable. It follows then, that unilateral angiography could have been expected to detect all the ipsilateral aneurysms (93) (assuming that the correct side were chosen), one-half the lateral plus anterior communicating aneurysms (36), and the double anterior communicating aneurysms (7). This amounts to 136 of the 449 double aneurysms (30 per cent) if the correct side were anticipated, or 20 per cent if the side were arbitrarily selected. Bilateral carotid

[1] It is usually the finding of the second aneurysm which has the greatest influence on the planning of treatment. Moreover, less than 5 per cent of multiple aneurysm cases have more than two aneurysms, and third aneurysms will probably be detected in about the same percentage as second aneurysms.

angiography, with the same assumptions, could have discovered all ipsilateral double aneurysms (93), all bilateral double aneurysms (211), all lateral plus anterior communicating aneurysms (104), and the 7 double anterior communicating aneurysms, amounting to 415/449 or 92 per cent.

The remaining 8 per cent of double aneurysm cases involve the posterior circulation and would require adequate vertebral angiography in addition to both carotids. Since multiple aneurysms occur in 20 to 25 per cent of aneurysm cases, the incidence of undetected double aneurysms among all aneurysm cases with only high quality bilateral carotid angiography amounts to approximately 2 per cent.[1]

Summary

1. The 6368 cases reported to the Central Registry of the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage over a seven year period serve as the basis for this study of natural history.

2. The population sample of the Cooperative Study has been considered in terms of how well it meets requirements for an ideal history study.

3. Intracranial aneurysm is the most common cause of subarachnoid hemorrhage (51 per cent), followed by hypertensive-arteriosclerotic cerebral vascular disease (15 per cent), cerebral arteriovenous malformations (6 per cent) and miscellaneous or multiple disease states (6 per cent). In 22 per cent of the cases, no cause could be determined by history plus angiography and/or autopsy.

4. Sixty-two (62) per cent of the cases with first subarachnoid hemorrhage (SAH) occurred between the ages of 40 and 64; the peak frequency for SAH due to aneurysm is 50 to 54; and for "other causes" (excluding AV malformations) it is 55 to 59. Among cases of first SAH due to arteriovenous malformations, 63 per cent occur between the ages of 20 and 49 without a prominent peak.

5. SAH from aneurysm is more common in women by a ratio of 3:2, but men predominate below age 40. Throughout most of the life span, SAH from arteriovenous malformations is slightly more common in men. The sex incidence of SAH of "other causes" is about equal from 20 to 70, but women preponderate increasingly thereafter. These data have been discussed with reference to the sex-incidence of hypertension and numerical ratio of the sexes in the population by decennial age groups.

6. The commonest specific single aneurysm site associated with SAH is the anterior communicating region (30 per cent), followed by the internal carotid-posterior communicating junction (24 per cent), and region of middle cerebral branchings (13 per cent). Of all single bleeding aneurysms, 37 per cent arise from the anterior cerebral systems, 36 per cent from the supracavernous internal carotids, 21 per cent from the middle cerebral systems, and 5.5 per cent from the vertebral-basilar system.

7. There are notable differences in sex incidence correlating aneurysm site and age groups. In general, internal carotid aneurysms occur more than twice as often in females, and this is the most probable site in women over the age of 20. Middle cerebral aneurysms also preponderate in women with a ratio of 3:2 .On the other hand, 58 per cent of anterior communicating aneurysms occur in men, and 41 per cent of all bleeding single aneurysms in men are at this site.

8. Analysis of signs and symptoms which preceded SAH show that only headache and "dizziness" had an incidence of at least 10 per cent. The data support the widely held impression that neither the cause of the hemorrhage nor the site of an aneurysm, if present, can be differentiated clinically except when an aneurysm is sufficiently large to produce neighborhood cranial nerve and other signs.

9. The relationship of environmental events to the onset of SAH has been considered. In one-third of the cases, SAH occurred during sleep or repose, and in another one-third, it occurred during random activity. Nonetheless, certain specified events showed a higher frequency of association than might be expected. Prominent among these were lifting and bending, emotional

[1] This figure might be as high as 3 or 4 per cent if angiography of the posterior circle had been more regularly implemented in the Study. Of the 69 per cent of cases in the double aneurysm study whose aneurysms were diagnosed by angiography exclusively, only 13 per cent had investigation of the vertebral-basilar system.

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10. The incidence of multiple aneurysms among 3321 cases of aneurysm was approximately 20 per cent. Of these, 3.5 per cent had three aneurysms, and 1.4 per cent had four or more.

11. Analysis of the site correlations among double aneurysms has proved that the hypothesis that the sites of the two aneurysms are independent of each other is untenable. Whatever the factors may be which determine the site distribution of single aneurysms, they are greatly outweighed for internal carotid, middle cerebral, and posterior circle aneurysms by a tendency to symmetrical aneurysms or the development of more than one aneurysm on the same vessel (or posterior circulation). Forty-seven (47) per cent of all double aneurysms were found to be contralateral to each other.

12. Of the three major aneurysm sites, anterior communicating aneurysms are least likely to be associated with a second aneurysm. When they are, the most probable site is middle cerebral. A second aneurysm in the same anterior communicating region is as probable as one on the posterior circulation.

13. When an aneurysm of the anterior circulation is identified in double aneurysm cases, the chances that the second aneurysm will arise from the posterior circulation is of the order of 3 to 5 per cent.

14. The effectiveness of various degrees of cerebral angiography in detecting multiple aneurysms has been calculated using the data for double aneurysms. Unilateral carotid angiography can be expected to discover 30 per cent of multiple aneurysm cases of the correct side is anticipated or 20 per cent if the side of angiography is arbitrarily selected. High quality bilateral carotid angiography will discover 92 per cent. The remaining 8 per cent of double aneurysm cases involve the posterior circulation and require adequate vertebral angiography in addition. However, as multiple aneurysms occur in only 20 to 25 per cent of aneurysm cases, the incidence of missed double aneurysms with high quality bilateral carotid angiography is about 2 per cent.

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